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Naval Health Research Center

Report No. 07-32

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Received 14 January 2008; Revised 13 March 2008; Accepted 15 March 2008

BACKGROUND: Women serving in the US military have some unique occupational exposures, including exposure to vaccinations that are rarely required in civilian professions. When vaccinations are inadvertently given during pregnancy, such exposures raise special concerns. These analyses address health outcomes, particularly preterm births and birth defects, among infants who appear to have been exposed to maternal smallpox vaccination in pregnancy. **METHODS:** This retrospective cohort study included 31,420 infants born to active-duty military women during 2003–2004. We used Department of Defense databases to define maternal vaccination and infant health outcomes. Multivariable regression models were developed to describe associations between maternal smallpox vaccination and preterm births and birth defects in liveborn infants. **RESULTS:** There were 7,735 infants identified as born to women ever vaccinated against smallpox, and 672 infants born to women vaccinated in the first trimester of pregnancy. In multivariable modeling, maternal smallpox vaccination in pregnancy was not associated with preterm or extreme preterm delivery. Maternal smallpox vaccination in the first trimester of pregnancy was not significantly associated with overall birth defects (OR 1.40; 95% CI: 0.94, 2.07), or any of seven specific defects individually modeled. **CONCLUSIONS:** Results may be reassuring that smallpox vaccine, when inadvertently administered to pregnant women, is not associated with preterm delivery or birth defects in liveborn infants. *Birth Defects Research (Part A) 82:533–539, 2008.* © 2008 Wiley-Liss, Inc.[†]

Key words: smallpox vaccine; vaccinia; maternal exposures; birth defects; preterm birth

INTRODUCTION

Maternal exposures during pregnancy have been reported to increase the risk of adverse reproductive outcomes such as preterm birth and birth defects (Brent, 2004; Goffinet, 2005; Friedman and Polifka, 2000; Scalli et al., 1995; Shepard, 1995). As the proportion of women serving in the US military increases, there are heightened concerns about the impact that military-unique exposures might have on reproductive outcomes (Fox et al., 1977; ASD/HA, 1999). The implementation of the National

[†]This article is a US Government work and, as such, is in the public domain in the United States of America.

Information in this article has been presented, in part, at the 10th Annual Force Health Protection Conference, August 7–11, 2008, in Louisville, KY, and at the 11th Annual Meeting of the National Birth Defects Prevention Network, February 11–13, 2008, in Washington, DC.
Grant sponsor: US Department of Defense; Grant number: 60504

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC.2003.0018).

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Published online 21 May 2008 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20470

Smallpox Vaccination Program by the United States government in early 2003 introduced a unique exposure to a large group of reproductive-aged military women (US Department of Health and Human Services, 2003). Although detailed documentation of the vaccine's short-term adverse health effects exists (Fox et al., 1977; Fenner et al., 1988; Rotz et al., 2001; Cono et al., 2003), the impact that maternal smallpox vaccination has on infant health is less well understood. Understanding such effects is important for clinicians caring for women inadvertently vaccinated during pregnancy (Napolitano et al., 2004).

Preterm birth is a frequent cause of infant death in the United States (Callaghan et al., 2006), and can result in long-term health problems in the surviving child (Reedy, 2007). While the rate of preterm delivery among military women is relatively low, some military occupational exposures, including prolonged standing, have been implicated as risk factors for preterm birth (Hatch et al., 2006; Magann et al., 2005). One recent report suggested that maternal vaccination during pregnancy is a potential risk factor for preterm birth (Orozova-Bekkevold et al., 2007); this finding was not associated with any specific vaccine and was subject to important limitations. Other, more authoritative, reviews do not support such a general association between maternal vaccination and preterm delivery (Brent, 2006; Munoz et al., 2005; Suzano et al., 2006). While smallpox (variola virus) infection during pregnancy is known to raise the rate of preterm birth (Nishiura, 2006), the impact of smallpox vaccine (vaccinia virus) on pregnancy outcomes remains largely unexplored.

Although the majority of birth defects have no known cause (Brent, 2004; Kalter and Warkany, 1983), some argue that receipt of a live virus vaccine during pregnancy might cause birth defects (Harley and Gillespie, 1972; Hanshaw and Dudgeon, 1978). Further, one report has suggested an association between smallpox vaccination in pregnancy and club foot malformations (Naderi, 1975). The biologic plausibility of such an association has been questioned, and the finding has not been reproduced in other epidemiologic studies (Cono et al., 2003; Greenberg et al., 1949). Further research may be helpful in reconciling conflicting reports on such rare outcomes.

There is a paucity of research concerning smallpox vaccine and reproductive health outcomes. Military-unique exposures, including deployments to wars, often cause great concern and resource-intensive research to address such concerns about birth defects among the children of military members (Erickson et al., 1984; Aschengrau and Monson, 1990; Briggs, 1995; Moehringer, 1995; Cowan et al., 1997; Kang et al., 2000; Araneta et al., 2003; Wells et al., 2006b; Doyle et al., 2006). The purpose of the present study was to examine the relationship between smallpox vaccination and preterm births, as well as smallpox vaccination and birth defects, among infants born to active-duty military women. This study complements the work of the National Smallpox Vaccine in Pregnancy Registry (CDC, 2003; Ryan et al., 2008) by evaluating a larger population of pregnancies resulting in live births, using electronic surveillance data.

METHODS

Population

Nearly 100,000 infants are born to US military families each year. Among these infants, 37% are born to Army members, 25% to Air Force members, 26% to Navy members, and 12% to members of the Marine Corps. Most infants are born to civilian wives of male service members; 18% of infants are born to active-duty women. US military births occur in all 50 states, in the District of Columbia, and in more than 20 foreign countries. The cohort for these analyses included all infants born to active-duty military women in the calendar years 2003 and 2004; a total of 35,501 infants potentially met these criteria. There were 159 infants with incomplete demographic information and 3,922 infants with inconsistent identifying information that made distinction from their siblings uncertain. A final cohort of 31,420 infants was included in analyses.

Data Sources

Data were obtained from multiple sources to capture all birth and health outcomes in the first year of life for infants born to military women in calendar years 2003 and 2004. Diagnostic *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) data were obtained by accessing electronic hospitalization and outpatient care records from all military and civilian facilities that provided care to members under the military healthcare system (Ryan et al., 2001). These records define birth defect diagnoses as well as diagnoses related to all coded medical care from birth to 12 months of age. Care that is outsourced from the military to civilian facilities, or otherwise billable to the military insurance system, is included in the accessed databases.

Military personnel systems were used to assess demographic and occupational history of parents. Variables obtained included: maternal race/ethnicity, date of birth, marital status, service branch, pay grade, and military occupation. Smallpox vaccination dates were determined through electronic vaccination records.

Outcomes

Estimated gestational age (EGA) was defined using ICD-9-CM codes. Preterm births were defined by ICD-9-CM 765.2x codes, with the maximum end of each range assigned as the infant's EGA at birth. For example, ICD-9-CM code 765.28 implies an EGA of 35–36 weeks; if this code was applied, the infant was assumed to be 36 weeks EGA at birth. If more than one five-digit code existed for a single infant, the most recently assigned code was used. If code 765.29 was assigned, 40 weeks EGA was assumed. If a 765.2x code was not assigned, then 765.0x and 765.1x codes were used to define EGA at birth. Infants assigned 765.0x were assumed to have reached 28 weeks EGA, and infants assigned 765.1x were assumed to have reached 36 weeks EGA. In the absence of the aforementioned codes, 40 weeks EGA was assumed.

Infants born to mothers vaccinated after 28 weeks EGA were excluded from the analyses of preterm delivery, because these infants would not have had the opportunity to be born as extremely premature after exposure to the vaccine. Additionally, multiple births were excluded from this portion of the analysis, because multiple gestation itself would confound the evaluation of preterm delivery.

Major birth defects were defined by the case definitions of the National Birth Defects Prevention Network (Sever, 2004), which include specific ICD-9-CM four- and five-

digit codes between 740.x and 760.x. Cases of atrial septal defect (745.5x) and patent ductus arteriosus (747.0x) in preterm infants were not coded as birth defects, in accordance with Metropolitan Atlanta Congenital Defects Program guidelines (Correa-Villasenor et al., 2003). In addition to these standard definitions of major birth defects, the code for club foot (754.7x) was added to separate analyses of specific defects, based on concerns from a prior report (Naderi, 1975). All healthcare utilization records up to 12 months after birth were assessed to capture all birth defects diagnosed in infancy. All diagnoses coded in inpatient records were considered valid. Diagnoses coded in outpatient records alone were required to appear on more than a single encounter to be considered valid. These validation criteria were developed based on reviews of original medical records within the military surveillance system (Ryan et al., 2001), as well as results of a validation review of cases in the Smallpox Vaccine in Pregnancy Registry (Ryan et al., 2008).

Statistical Analyses

Analyses included descriptive investigations of demographic and occupational characteristics stratified by maternal smallpox vaccination status. Preliminary univariate analyses, including chi-square and *t* tests, were performed to assess the significance of associations between the outcomes of interest and exposure. An exploratory model analysis was completed to assess regression diagnostics, significant associations, colinearity, and possible confounding, while simultaneously adjusting for all other variables in the model. Evaluation of gestational age at birth as a polychotomous outcome was conducted using three levels: extreme preterm birth (≤28 weeks EGA), preterm birth (28–36 weeks EGA), and full-term birth (>36 weeks EGA).

Multivariable logistic regression models were used to estimate the adjusted ORs and 95% CIs of birth defects among infants with the exposure of concern. The models used generalized estimating equations to account for correlated outcomes among multiple births (Liang and Zeger, 1986); such births included siblings from different pregnancies as well as twins. For the rare outcomes of specific birth defects, the OR was estimated using exact logistic regression. A statistical correction for multiple comparisons was also applied to the analyses of specific defects. When available, models were adjusted for multiple birth, infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal branch of service, maternal pay grade, and maternal military occupation. Military demographic variables were selected to represent some measure of socioeconomic status. Variables were included in modeling based on potential confounding due to past reported associations with birth defects (Yang et al., 2008). ORs were considered to approximate risk ratios and, in all models, risk ratios were similarly calculated to ensure that point estimates of association and statistical significance were not changed. All statistical analyses were performed using SAS software (Version 9.1.3; SAS Institute, Inc., Cary, NC).

The primary analysis of birth defects examined infants born to mothers vaccinated against smallpox in the first trimester compared to infants born to mothers vaccinated outside of the first trimester. Current Centers for Disease Control and Prevention guidelines recommend that women avoid becoming pregnant for 4 weeks (28 days) following receipt of the smallpox vaccine to ensure viral shedding is complete prior to conception (Wharton et al., 2003). Using the definitions of EGA defined previously, the exposure window for first trimester vaccination began 4 weeks prior to the first day of EGA of pregnancy and ended at 13 weeks EGA. Referent groups for the primary models included women vaccinated outside the first trimester of pregnancy, rather than never-vaccinated women. This was applied due to concerns that never-vaccinated women might be less comparable, perhaps less healthy, because they were waived from being ready for military deployment (Sato et al., 2002; Wells et al., 2006a). Alternative models were evaluated, defining the referent population as infants born to women vaccinated postpregnancy or infants born to never-vaccinated women.

RESULTS

Among 31,420 infants born to military women during 2003–2004, a total of 672 infants appeared to be born to women who received smallpox vaccine during the first trimester of pregnancy (Table 1). There were 7,063 infants born to women who received smallpox vaccine outside of the first trimester; 210 of these infants appeared exposed to maternal vaccine in late pregnancy, 2,782 infants' mothers were vaccinated before pregnancy, and 4,071 infants' mothers were vaccinated only after giving birth. There were 23,685 infants born to military women in 2003–2004 who had no record of ever receiving smallpox vaccine.

Table 1 describes birth characteristics and maternal demographic characteristics for all infants born to military women in 2003–2004. No increased proportional differences were observed between infants exposed to maternal smallpox vaccination and plurality (singleton or multiple), or between infants exposed to maternal smallpox vaccination and infant gender. Never-vaccinated mothers differed slightly, but significantly ($p < .05$), from vaccinated mothers in that never-vaccinated women tended to be older, of white race/ethnicity, married, serving in the Air Force or Navy, and of officer rank.

More than 90% of all singleton infants appeared to be born full term. For models of gestational age at delivery, 1,845 infants were considered preterm (374 defined as preterm by ICD-9-CM code 765.1x and 1,471 defined by ICD-9-CM code 765.2x on gestational age), and 226 infants were considered extremely preterm (76 defined as extremely preterm by ICD-9-CM code 765.0x and 150 defined by ICD-9-CM code 765.2x on gestational age). Maternal smallpox vaccination was not associated with preterm delivery (OR 1.19; 95% CI: 0.89, 1.58) or extreme preterm delivery (OR 0.84; 95% CI: 0.33, 2.14) in the primary model. Likewise, in models with alternative referent groups, maternal vaccination in pregnancy was not associated with preterm or extreme preterm delivery. Detailed results are shown in Table 2.

Thirty infants (4.5%) exposed to maternal smallpox vaccine in the first trimester had at least one major birth defect defined by ICD-9-CM coding in the first year of life. Birth defects occurred among 3.7% of infants born to women vaccinated prepregnancy, and 3.2% of infants born to women vaccinated postpregnancy. Using multivariable logistic regression, adjusting for infant plurality, infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal service branch, pay

Table 1
Characteristics of Infants Born to US Military Women in 2003–2004, by Maternal Smallpox Vaccination Status

	Maternal vaccination										
	Never vaccinated		Prepregnancy		1st trimester		2nd or 3rd trimester		Postpregnancy		Total
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*
Total	23,685	(100.0)	2,782	(100.0)	672	(100.0)	210	(100.0)	4,071	(100.0)	31,420
Infants with birth defects											
No	22,818	(96.3)	2,680	(96.3)	642	(95.5)	200	(95.2)	3,941	(96.8)	30,281
Yes	867	(3.7)	102	(3.7)	30	(4.5)	10	(4.8)	130	(3.2)	1,139
Gestational age											
Full-term	22,016	(93.0)	2,541	(91.3)	621	(92.4)	195	(92.9)	3,808	(93.5)	29,181
Preterm	1,486	(6.3)	218	(7.8)	48	(7.1)	13	(6.2)	234	(5.7)	1,999
Extreme preterm	183	(0.8)	23	(0.8)	3	(0.4)	2	(1.0)	29	(0.7)	240
Infant plurality											
Singleton	23,441	(99.0)	2,742	(98.6)	672	(100.0)	210	(100.0)	4,025	(98.9)	31,090
Multiple	244	(1.0)	40	(1.4)	0	0	0	0	46	(1.1)	330
Infant gender											
Female	11,645	(49.2)	1,356	(48.7)	335	(49.9)	110	(52.4)	1,977	(48.6)	15,423
Male	12,040	(50.8)	1,426	(51.3)	337	(50.1)	100	(47.6)	2,094	(51.4)	15,997
Maternal age											
Younger than 35	21,907	(92.5)	2,634	(94.7)	650	(96.7)	207	(98.6)	3,874	(95.2)	29,272
35 and older	1,778	(7.5)	148	(5.3)	22	(3.3)	3	(1.4)	197	(4.8)	2,148
Maternal race/ethnicity											
White	11,890	(50.2)	1,317	(47.3)	315	(46.9)	116	(55.2)	1,698	(41.7)	15,336
Black	7,237	(30.6)	895	(32.2)	209	(31.1)	56	(26.7)	1,520	(37.3)	9,917
Hispanic	2,592	(10.9)	362	(13.0)	97	(14.4)	23	(11.0)	489	(12.0)	3,563
Asian	1,011	(4.3)	108	(3.9)	24	(3.6)	9	(4.3)	200	(4.9)	1,352
Other/unknown	955	(4.0)	100	(3.6)	27	(4.0)	6	(2.9)	164	(4.0)	1252
Maternal marital status											
Married	16,435	(69.4)	1,696	(61.0)	352	(52.4)	148	(70.5)	2,656	(65.2)	21,287
Unmarried	7,250	(30.6)	1,086	(39.0)	320	(47.6)	62	(29.5)	1,415	(34.8)	10,133
Maternal branch of service											
Army	7,055	(29.8)	1,301	(46.8)	388	(57.7)	97	(46.2)	1,626	(39.9)	10,467
Navy	7,631	(32.2)	649	(23.3)	88	(13.1)	53	(25.2)	659	(16.2)	9,080
Air Force	7,448	(31.4)	718	(25.8)	155	(23.1)	16	(7.6)	1,571	(38.6)	9,908
Marine Corps	1,551	(6.5)	114	(4.1)	41	(6.1)	44	(21.0)	215	(5.3)	1,965
Maternal pay grade											
Enlisted	20,702	(87.4)	2,517	(90.5)	625	(93.0)	194	(92.4)	3,751	(92.1)	27,789
Officer	2,983	(12.6)	265	(9.5)	47	(7.0)	16	(7.6)	320	(7.9)	3,631
Maternal military occupation											
All other	17,654	(74.5)	2,026	(72.8)	512	(76.2)	140	(66.7)	3,301	(81.1)	23,633
Healthcare	4,271	(18.0)	518	(18.6)	114	(17.0)	56	(26.7)	490	(12.0)	5,449
Combat	1,760	(7.4)	238	(8.6)	46	(6.8)	14	(6.7)	280	(6.9)	2,338

grade, and occupation, maternal smallpox vaccination during the first trimester of pregnancy was associated with an OR of 1.40 for infants having at least one major birth defect when compared to those vaccinated outside of the first trimester (95% CI: 0.94, 2.07) (Table 3). This finding was not statistically significant at $\alpha = .05$.

In alternative models, infants born to women vaccinated only postpregnancy and infants born to never-vaccinated women were considered the referent groups. Infants born to women in other vaccinated groups were compared to these referent groups, and adjusted odds of birth defects are shown in Table 3. No statistically significant associations were observed between maternal smallpox vaccination and birth defects in liveborn infants.

Specific types of birth defects among infants exposed to maternal smallpox vaccine in the first trimester were compared with infants born to other vaccinated women. Multivariable regression analyses were performed for each defect with three or more cases in both the exposed and referent groups, and for club foot defects (Table 4). No statistically significant findings were observed in these analyses when models were adjusted for multiple comparisons. If adjustment for multiple comparisons was not applied, the model of atrial septal defect would have a statistically significant association with exposure (OR 2.62; 95% CI: 1.21, 5.68).

Finally, all multivariable models for preterm delivery and birth defects were compared to unadjusted models. Crude ORs did not differ substantially from adjusted ORs, and indications of statistical significance did not change in any model (detailed results not shown). Additionally, when infants with missing or inconsistent demographic information were included in analyses, overall measures of association between the exposure and outcomes were unchanged.

DISCUSSION

Selected health outcomes were examined among infants born in 2003 and 2004 to military women who

Table 2
Adjusted ORs* for Preterm and Extreme Preterm Birth among Singleton Infants Born to Women Who Received Smallpox Vaccine during Pregnancy, with Alternative Models

Characteristic	Preterm†		Extreme preterm†	
	OR	95% CI	OR	95% CI
Primary model				
Maternal vaccination pre- or postpregnancy (reference)	1.00	—	1.00	—
Maternal vaccination during pregnancy	1.19	(0.89, 1.58)	0.84	(0.33, 2.14)
Alternative model a				
Maternal vaccination postpregnancy (reference)	1.00	—	1.00	—
Maternal vaccination during pregnancy	1.35	(0.99, 1.84)	0.76	(0.28, 2.06)
Alternative model b				
No maternal vaccination (reference)	1.00	—	1.00	—
Maternal vaccination during pregnancy	1.32	(1.00, 1.74)	0.88	(0.36, 2.17)

*Polychotomous logistic regression models were adjusted for the following variables: infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal branch of service, maternal pay grade, and maternal military occupation.
†Extreme preterm defined as ≤28 weeks EGA at birth. Preterm defined as 28–36 weeks EGA at birth. The reference group for the outcome variable of these polychotomous logistic regression models was full-term birth.

received smallpox vaccine. No statistically significant associations were observed between maternal smallpox vaccination and preterm birth or birth defects. Although a small increased OR for overall birth defects was observed after first trimester maternal vaccination, this finding was not statistically significant. Additionally, contrary to earlier suggestions by Naderi (1975), infants born to women who received smallpox vaccine in pregnancy did not have a significantly increased risk of club foot deformities. Interpretation of any analysis of specific defects remains challenging due to very small numbers of cases.

This study served as a complementary analysis to evaluations from the National Smallpox Vaccine in Pregnancy Registry (CDC, 2003; Ryan et al., 2008). More cases of maternal exposure in pregnancy were identified in these analyses than in the Registry. This is not unexpected, because the Registry relies on provider reporting to capture cases and these analyses leveraged the larger military electronic databases to capture exposures. Among the infants that appeared in both the Registry and these analyses, there was good agreement between EGA dates and maternal vaccination dates, as well as good agreement among the infant outcomes evaluated here. An important feature of the Registry, despite its lower case capture, is the ability to evaluate pregnancy losses. Losses are clearly critical outcomes in the spectrum of reproductive health, yet they are not well captured in electronic database analyses. The Registry also has the unique value of potentially identifying any cases of fetal vaccinia, a very rare but previously well described outcome of fetal infection from the vaccine virus (Cono et al., 2003; Green et al., 1966; Harley and Gillespie, 1972).

An important limitation to these analyses is the inability to evaluate other maternal exposures that may affect outcomes, such tobacco, alcohol, medications, prolonged standing, or other occupational stressors. These exposures may all be more common in later recognized pregnancies and associated with the outcomes of preterm delivery and birth defects (Carmichael et al., 2002; Goffinet, 2005). Importantly, late recognition of pregnancy may also be a fundamental difference between cases of inadvertent vaccination in pregnancy and cases of vaccine deferral until after pregnancy. Because the inability to adjust for such factors would tend to artificially

Table 3
Adjusted ORs* for Birth Defects among Infants Born to Military Women, by Maternal Smallpox Vaccination Status, 2003–2004

	Referent group for maternal vaccination					
	Primary model		Alternative models			
	Referent group: Vaccinated outside of 1st trimester		Referent group: Vaccinated postpregnancy		Referent group: Never vaccinated	
Exposure groups with associated OR and 95% CI	1st trimester vaccinated	1.40 (0.94, 2.07)	1st trimester vaccinated	1.46 (0.96, 2.23)	1st trimester vaccinated	1.24 (0.85, 1.81)
			Pre-pregnancy vaccinated	1.15 (0.87, 1.52)	Pre-pregnancy vaccinated	1.01 (0.82, 1.25)
			Late-pregnancy vaccinated	1.52 (0.73, 3.15)	Late-pregnancy vaccinated	1.30 (0.68, 2.49)
					Post-pregnancy vaccinated	0.88 (0.73, 1.07)
					Ever-vaccinated	0.97 (0.84, 1.12)

*Logistic regression models were adjusted for infant plurality, infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal service branch, maternal pay grade, and maternal military occupation.

Table 4
Occurrence of Selected Birth Defects among Infants Born to Military Women Who Received Smallpox Vaccine in the First Trimester of Pregnancy

	Unexposed cases n = 7,063		Exposed cases n = 672		Adjusted ORs of association*	
Specific defect	n	%	n	%	OR	95% CI
Atrial septal defect†	35	(0.50)	8	(1.19)	2.62	(0.91, 7.56)
Ventricular septal defect	41	(0.58)	4	(0.60)	1.03	(0.15, 3.61)
Patent ductus arteriosus†	35	(0.50)	3	(0.45)	0.90	(0.09, 3.86)
Pulmonary valve atresia or stenosis	17	(0.24)	4	(0.60)	2.48	(0.33, 16.51)
Hypospadias or epispadias‡	38	(0.54)	3	(0.45)	0.97	(0.09, 4.61)
Congenital hip dislocation	9	(0.13)	3	(0.45)	3.55	(0.28, 38.66)
Club foot§	10	(0.14)	2	(0.30)	2.04	(0.08, 13.80)

*The referent group (unexposed) includes infants born to women vaccinated outside the first trimester of pregnancy. Logistic regression models were adjusted for infant plurality, infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal service branch, maternal pay grade, and maternal military occupation, when available. Confidence limits represent correction for multiple comparisons.

†Excluding preterm cases of atrial septal defect and patent ductus arteriosus.

‡Analysis restricted to male infants.

§Adjusted for infant gender using exact logistic methods.

increase any observed associations in this study, the lack of statistically significant findings in these analyses may be even more reassuring.

Additional limitations of this study relate to reliance on electronic databases for both maternal and infant information. Infant medical diagnoses from electronic databases include some degree of miscoding, and validation efforts cannot completely mitigate this challenge. Similarly, estimation of EGA based on coding of birth records is likely to introduce some degree of error. Although we cannot verify this assumption, errors introduced by miscoding in infant and birth records may be assumed to be nondifferential with regard to maternal vaccination status.

Despite limitations, this study is the first in more than 50 years to examine the specific birth outcomes of preterm birth and birth defects in a large group of infants exposed to smallpox vaccine *in utero*. One strength of this study is related to access to databases containing all available medical diagnoses during the first year of life, allowing for nearly complete capture of birth defect diagnoses, including those that present weeks or months after delivery. Leveraging military databases for demographic and exposure information provides consistent measures that eliminate the potential for recall bias. Similarly, the ability to access extensive demographic information from the well-defined military population allowed adjustment for many potential confounding variables in statistical modeling. Finally, conclusions may be strengthened by their consistency across models that applied alternative referent groups.

The United States Department of Defense has a responsibility to monitor and protect the health of service members and their families. The enactment of a compulsory smallpox vaccination policy introduced a unique occupational exposure to a large group of reproductive-aged service members. This investigation provides critical information, not available from other populations, on the effect of maternal smallpox vaccination on birth defects and preterm birth among liveborn infants. Although results are reassuring that maternal vaccination is not associated with these adverse outcomes, evaluations of the full spectrum of reproductive health outcomes after smallpox vaccination should continue.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of the following professionals: Dr. Renata Engler, Dr. Karl Friedl, Dr. John Grabenstein, Dr. Gregory Gray, Dr. Roberta Ness, and Dr. Gregory Poland. We also appreciate the work of Mr. Scott Seggerman from the Defense Manpower Data Center, and the support of the Henry M. Jackson Foundation for the Advancement of Military Medicine.

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REPORT DOCUMENTATION PAGE

1. Report Date (DD MM YY)
02/08/07

2. Report Type
New

3. DATES COVERED
CY 2003 – CY 2004

4. TITLE AND SUBTITLE
Evaluation of Preterm Births and Birth Defects in Liveborn Infants of US Military Women Who Received Smallpox Vaccine

5a. Contract Number:
5b. Grant Number:
5c. Program Element:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 60504

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Naval Health Research Center
P.O. Box 85122
San Diego, CA 92186-5122

9. PERFORMING ORGANIZATION REPORT NUMBER
Report No. 07-32

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
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10. Sponsor/Monitor's Acronyms(s)
NMRC/NMSC

11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT (maximum 200 words)

Background: Women serving in the US military have some unique occupational exposures, including exposure to vaccinations that are rarely required in civilian professions. When vaccinations are inadvertently given during pregnancy, these exposures raise special concerns. These analyses address health outcomes, particularly preterm births and birth defects, among infants who appear to have been exposed to maternal smallpox vaccination in pregnancy.
Methods: This retrospective cohort study included 35,342 infants born to active-duty military women during 2003-2004. We used Department of Defense databases to define maternal vaccination and infant health outcomes. Multivariable regression models were developed to describe associations between maternal smallpox vaccination and preterm births and birth defects in liveborn infants.
Results: There were 8,588 infants identified as born to women ever vaccinated against smallpox, and 770 infants born to women vaccinated in the first trimester of pregnancy. In multivariable modeling, maternal smallpox vaccination in pregnancy was not associated with preterm or extreme preterm delivery. Maternal smallpox vaccination in the first trimester of pregnancy was not associated with overall birth defects (odds ratio, 1.28; 95% confidence interval: 0.93, 1.78), or any of five specific defects individually modeled.
Conclusion: Results may be reassuring that smallpox vaccine, when inadvertently administered to pregnant women, is not associated with preterm delivery or birth defects in liveborn infants.

15. SUBJECT TERMS
smallpox vaccine, vaccinia, maternal exposures, birth defects, preterm birth

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b.ABSTRACT	b. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	8	19b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429